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Human Cancers and Viruses: A Hypothesis for Immune Destruction of Tumours Caused by Certain Enveloped Viruses Using Modified Viral Antigens

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Abstract—Certain viruses which have been identified as possible aetiological agents of human malignant tumours have 2 common characteristics: a) they persist in the human body for long periods despite the presence of antibodies to them and b) they all possess viral envelopes. The envelopes, consisting of phospho-lipoproteins are derived from host cells viz nuclear envelope in the case of DNA viruses, and the cell membrane in the case of RNA viruses. These host cell elements on the viral envelope modify the antigenicity of the specific surface antigens which are now perceived by the host immune system as partly self. This in turn blackmails the immune system, if it is to avoid serious auto-immune disease, into producing compromise and ineffective antibodies. The hypothesis proposes the dissolution of the viral envelope in vitro and the re-introduction of the viral core into the host. This should provoke a new uncompromised immune response because it will be directed at the viral core only. This response should eliminate the viral core and with it, the whole enveloped virus; as well as the malignant tumour cells which carry the viral genome derived essentially from the viral core. This approach should introduce a new method for treating and preventing tumours caused by enveloped viruses and the chronic diseases caused by such viruses.

Introduction

Several human malignant tumours have so often been associated with certain specific viruses that an aetiological role has been assigned to such viruses. Among these tumours and viruses may be mentioned:

1. Burkitt's lymphoma (1) and nasopharyngeal carcinoma and the Epstein Barr virus (EBV) (2)
2. Carcinoma of the cervix and herpes virus type 2 (HV2) (3) and more recently the human papilloma virus (HPV) (4)
3. Kaposi's sarcoma and the cytomegalo-virus (CMV) (5)
4. Primary liver cancer and hepatitis B virus (HPV) (6, 7)

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5. More recently the human T-cell leukaemia and the human *T-cell leukaemia virus* (HTLV I) (8).

It is probable that further research will show that other viruses are implicated in other human tumours as well.

The evidence linking the above viruses to these malignant tumours has come partly from epidemiological studies and partly from molecular biology. Epidemiological studies have shown a higher incidence of the tumour concerned in social groups or in geographical areas of high viral endemicity than in those of low viral endemicity. The incidence of primary liver cancer for example, is 50 times higher in Africa and Asia where the prevalence of the hepatitis B antigen is higher than in North America and Northern Europe where this antigen is low (7). Seroepidemiology has also shown significantly higher antibodies or viral antigen in tumour patients than in normal controls living in the same areas.

At the molecular level the Epstein-Barr virus has transformed normal lymphocytes in vitro into cells that have all the characteristics of Burkitt Lymphoma cells (9), and the viral genome has been detected in tumour cells (10) further supporting the direct involvement of the virus in this tumour.

Although these tumour viruses are indeed involved in the malignant transformation of the affected cells, given the high endemicity of the viruses in the various communities concerned, and the relative absence of malignant tumours in most of those who have had contact with the virus, it can be readily admitted that other additional factors in the host or the environment must play a determinant role in those who eventually develop malignant tumours. Such factors would include for example, the presence of aflatoxin or alcoholism in association with hepatitis B in liver cancer (11) or the presence of endemic malaria with the Epstein Barr Virus in Burkitt's lymphoma (12).

These other factors notwithstanding, understanding the relationship of the viruses to the host is indispensable for the proper understanding of these tumours.

Given the complexity of the problem and the great volume of publications on cancer and viruses, a simplified approach will hopefully attempt to perceive the common thread running through this complex problem which could, in turn, shed new light on it.

The tumour viruses

Although the above tumour viruses differ from one another in some respects, (5 of the above group are DNA viruses, 3 of which belong to the herpes group alone, and one is an RNA virus) they all share 2 important characteristics:

1. they all persist in a latent or overt forms in the body for long periods, sometimes for life, and
2. they all possess viral envelopes.

These 2 common characteristics must play a vital role in their common oncogenicity. A virus that could persist in the body for long periods, will surely have a greater chance of interfering with the genetic material of the host cell and so increase its chances of transforming such a cell into a malignant tumour cell, than one that was easily and completely eliminated from the body.

A proper understanding of how the above 2 characteristics are related to each other and to the host could throw new light on the subject of viruses and malignant tumours. Such information is indispensable for formulating action that is directed at eliminating malignant tumours caused by them.

The persistence of the viruses in the body

No satisfactory explanation has been given for the long persistence of the above viruses. If antibodies do not eliminate the viruses against which they were produced, whatever the explanations for this might be, it can be concluded that the antibodies in question are ineffective. Why indeed are such antibodies ineffective?

The quality of effectiveness of the antibodies produced in a body depends on one or both of the following 2 factors:

1. The competence of the immune system of the host.
2. The nature of the antigens provoking them.

Since most patients with these persistent viruses have no obvious stigmata of a pre-existing immune incompetence or depression, one must conclude that it is in the nature of these viruses to provoke 'ineffective' antibodies. What then is in the *nature* of these viruses that enables them to provoke ineffective antibodies?

It should be recalled in passing, that immunity to the *hepatitis A virus infection*, a non-enveloped virus, for example, is effective and those who survive the initial infection eliminate the virus from the body completely. In contrast, those with hepatitis B virus infection, an enveloped virus, frequently have persistence of the virus.

The viral envelope

Since all of the above different tumour viruses possess a viral envelope, it is probably the *envelope* that enables them to provoke ineffective antibodies.

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The DNA viruses in the above group develop, as is well known, in the nucleus of the infected cell and acquire their envelopes from the inner lamella of the nuclear membrane of the infected cell (13). The complete viruses leave the cell with their envelopes in place. Specific surface viral antigens, mostly glycoproteins, are attached to the surface of the envelope.

The HTLV I, an RNA virus, in keeping with the development of retro-viruses, acquires its envelope by budding from the cell surface membrane. Specific surface viral antigens made of glycoproteins, are also attached to, or project from, the surface of the viral envelope.

In both the DNA and RNA viruses, the envelope which has the same basic form, is made of phospholipoproteins which are derived, as was indicated above, from the host cell. Being of host cell origin, the viral envelope is itself non-antigenic. However, in carrying the specific surface antigens of the virus, the envelope becomes part of the antigenic complex which the viral surface presents to the immune system of the body. It is this antigenic complex—host lipoproteins in the envelope plus specific surface antigens—which determines the immune response of the body.

The presence of the envelope modifies the specific surface antigens

The antigenic complex described above is interpreted by the host immune system as partly self because the envelope is of host origin. The virus, using the envelope, has thus effectively 'disguised' itself and has induced or misled the immune system into considering it, with its surface antigens as partly self.

If the immune response, humoral or cell-mediated, were to destroy the antigenic complex as constituted, it would also do serious harm to those host cell elements—whether infected or not, from which the envelope was derived. This would constitute a serious auto-immune disease.

To avoid such serious damage, the immune system produces instead 'compromise' antibodies which in order not to destroy its own cells, do not also destroy the virus (these compromise antibodies nevertheless cause some degree of auto-immunity which can be demonstrated in various ways in many such patients). Thus the virus, using the non-antigenic lipoproteins of the envelope as a kind of disguise has 'blackmailed' the immune system into producing a compromising and therefore ineffective, response thereby ensuring its survival in the body. Disguise and blackmail have been the modus operandi of these enveloped viruses.

The foregoing over-simplified account provides the elements of a hypothesis for ridding the body of the above enveloped viruses and eventually of the malignant tumours caused by them.

Hypotheses

The hypothesis proposes in brief that the viral envelope be removed with lipid solvents (ether or chloroform) or an appropriate enzyme in vitro and the naked viral core obtained be re-injected into the host. The new core antigens thus exposed, should provoke an uncompromised immune response because they will be directed at the viral core only and this should, in theory, eliminate the virus from the body. The purpose of this method is to transform an enveloped virus into a non-enveloped antigen. The action of the lipid solvent should therefore be limited to dissolving only the envelope; prolonged action may damage the core antigens.

Whilst viral nucleic acids are infective and can cause viral multiplication when introduced into the cell, the natural infectivity of the enveloped viruses vis a vis the cell, is abolished when it is deprived of its envelope. It should then act as a simple antigenic material.

Verification of the hypothesis should lead to several useful applications in practice. Before considering such possible applications however, it is necessary to answer two possible theoretical objections to the hypothesis.

Possible objections to the hypotheses

The first of these objections concerns the suggestion that the lipoproteins of the envelope can indeed modify the specific surface antigens of the virus to the point of misleading the immune system into considering the envelope and its specific surface antigens as partly self.

It will be recalled that Freund's complete adjuvants were widely used in immunology in the 1950–1970s to enhance the antigenicity of various protein antigens. These adjuvants were made partly from lipid extracts of the tubercle bacillus, paraffin and oils of various kinds. How these adjuvants worked in the body was never very clear. What was clear however, was that without being antigenic themselves, they nevertheless enhanced the antigenicity of those antigens with which they were introduced into experimental animals or patients.

The lipoproteins on the viral envelope are lipids also and can also be expected to have an adjuvant or enhancing effect on the specific surface antigens

on the viral envelope, and this should provoke strong antibodies.

Yet the hypothesis proposes instead that the lipoproteins of the envelope modify and reduce the antigenicity of the specific surface antigens which in turn provoke weak or ineffective antibodies. The reason for this is that the lipids of the envelope are of host origin and not foreign to the body as was the case with the crude adjuvants of 4–5 decades ago. By associating the host lipoproteins with its surface antigens The virus has transformed antigens which should have been enhanced and so eliminated into antigens that are 'tolerated' by the immune system. There is a useful message for transplantation immunologists hidden somewhere in this simple but effective viral disguise of its foreign antigens.

The second possible objection to the hypothesis concerns the new immune response that is expected when the viral core, shorn of its envelope, is re-introduced into the host. Why, it could be asked, should the immune system react anew to an antigen with which it has apparently been in contact previously?

In the synthesis of the above enveloped viruses and indeed of all such viruses, defective particles are frequently produced consisting of naked cores of or empty envelopes only. Such defective cores, by that very fact, are different from the cores of complete enveloped viruses, otherwise they would not have been defective. Also, when complete enveloped viruses degenerate and die, as they eventually must, they release damaged or degenerating cores. These defective or degenerated cores, (HBe, HBc and the antibodies to them are sometimes found, for example, in primary liver cancer associated with hepatitis B virus (14)) will continue to be produced for as long as viral synthesis and degeneration continue.

These defective or degenerating cores are clearly different, in some very small but important detail, from the intact core of a complete virus and their respective antigenicities must clearly be different also. Since there is no natural mechanism for artificially dissolving the viral envelope in vivo, it can be assumed that the immune system of the host has never had any previous contact with the normal core of a complete virus. The viral core obtained in vitro must therefore constitute a truly new antigen for the host capable, when re-introduced into the body, of provoking a completely new immune response which should eliminate the core of the complete enveloped virus from the body—which is the only part of the virus worth eliminating.

In the light of the foregoing it should now be interesting to examine the consequences of the elimination of the intact viral core on the corresponding malignant tumour.

The malignant tumour

Several malignant tumours caused by enveloped viruses have been shown to contain the corresponding viral genome on the tumour cells, zur Hausen et al (10) as stated above, have shown, for example, the EBV DNA in biopsies of Burkitt's tumour and anaplastic carcinoma of the nasopharynx.

If antibodies to the EBV, have been unable to eliminate the EBV from Burkitt's lymphoma patients because of the 'blackmailing' presence of the viral envelope, it is not surprising that the same antibodies should be unable, for the same reason, to act against the viral DNA present in the tumour cells.

The new uncompromised immune response provoked by the intact viral core as indicated above, should eliminate that core of genome in the enveloped virus and whatever else it may be. This would include the viral genome on the tumour cell which will, in consequence, be destroyed as well. This immune destruction should also include all other non-malignant cells that carry the viral genome. In the case of primary liver cancer associated with the hepatitis B virus for example, this could include non cancerous virally infected liver cell. Unless adequate measures are taken, the immune destruction of the tumour could therefore lead to serious consequences in such patients.

In contrast, cancer of the cervix, with the non-type 2 infection or even the more recent HPV related to the cervix and lower genital tract, should give excellent results.

Conclusion

Confirmation of the hypotheses should introduce a new era in the treatment of the above enveloped viruses and the tumours caused by them. By introducing into the host the intact viral core obtained in vitro from a complete enveloped virus, one can induce a competent immune system to completely eliminate the viruses concerned from the body. The same approach could be used for all other enveloped viruses since all such enveloped viruses are constructed on the same basis. These will include, in addition to those mentioned above, most of the viruses that cause disease in man and animals, the viruses of acquired immune deficiency syndrome of man (AIDS) and animals, the slow retroviruses of animals such as scrapie in sheep, (15) caprine encephalitis in goats, (16) equine infectious

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EIA in horses (17) etc. Tumours caused by enveloped oncogenic retroviruses of animals and man could be eliminated also.

Simple and effective vaccines based on the same principle could of course, be used to prevent infections in healthy persons or animals by enveloped viruses and the chronic diseases and malignant tumours induced by them. This should bring great benefits to animal and human health.

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